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ORIGINAL RESEARCH

Extravasation associated with cancer drug therapy: multidisciplinary guideline of the Japanese Society of Cancer Nursing, Japanese Society of Medical Oncology, and Japanese Society of Pharmaceutical Oncology

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Background: Extravasation (EV), or the leakage of anticancer drugs into perivascular and subcutaneous tissues during intravenous administration, can cause serious conditions that may require surgical intervention. Therefore, updated guidelines for EV based on systematic review are needed. Additionally, classifications for anticancer drugs that cause EV are not standardized across the current guidelines, and some novel drugs have not been classified. Therefore, this study aimed to formulate guidelines using evidence-based information for shared decision making on prevention, early detection, treatment, and care for EV in Japan and provide additional classification for tissue injury based on systematic review.

Materials and methods: The members of the Japanese Society of Cancer Nursing (JSCN), Japanese Society of Medical Oncology (JSMO), and Japanese Society of Pharmaceutical Oncology (JASPO) were surveyed about significant clinical challenges related to EV, and 17 clinical questions (CQs) were formulated. PubMed and ICHUSHI Web were searched using the Patient, Intervention, Comparison, and Outcomes terms listed in each CQ as key words. For the classification of new drugs, articles published through February 2021 were selected using the search terms 'extravasation', 'injection-site reaction', 'adverse events', and the names of individual drugs as key words.

Results: Recommendations based on the results of randomized controlled trials (RCTs) were made with regard to the selection of central venous (CV) devices (CQ2, CQ3a, CQ3b, and CQ3c), regular replacement of peripheral venous catheters (CQ5), and use of fosaprepitant (CQ7). These CQs are novel and were not mentioned in previous guidelines. Warm compression monotherapy (CQ10b) and local injection of steroids (CQ12) are discouraged for the management of EV. Ten new drugs were classified for EV tissue injury.

Conclusions: This study provides updated guidelines for the prevention and treatment of EV, which can be used to help health care providers and patients and their families practice better EV management.

Key words: extravasation, chemotherapy, injection-site reaction, adverse events, clinical practice guideline

INTRODUCTION

Extravasation (EV) is the leakage of anticancer drugs into the perivascular and subcutaneous tissues during intravenous administration.[1] EV can cause redness, swelling, pain, burning sensation, erosion, and blisters on the skin and surrounding tissues, and it sometimes causes ulceration, tissue necrosis, and other serious skin conditions that require surgical intervention.[2] EV occurs in 0.1%-6.5% of patients receiving anticancer drugs.[3] Although the overall incidence of EV is extremely low, many patients are at risk of EV, since it is caused by widely prescribed anticancer drugs.[2]

Anticancer drugs are classified as vesicants, irritants, or non-vesicants based on their potential to cause tissue injury by skin necrosis (Supplementary Table S1, available at

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https://doi.org/10.1016/j.esmoop.2024.103932).[2,4] Vesicants can cause tissue necrosis or formation of blisters. Irritants and non-vesicants are associated with a lower risk of necrosis unless leakage in large quantities occurs; however, they still pose a risk of tissue destruction and can cause inflammation and pain. Therefore, prevention of EV is important for all drugs.

Although prevention, diagnosis, treatment, and care of EV are important, there is limited evidence about the optimal procedures. Multiple guidelines for EV have been published.[2,5-7] However, no EV guideline has been based on a systematic review. Additionally, the classification of tissue injury from anticancer drugs differs between guidelines, which is an important issue in assessing the risk of EV. Therefore, this study aimed to formulate guidelines using evidence-based information for shared decision making on prevention, early detection, treatment, and care for EV in Japan and provide additional classification for tissue injury based on a systematic review.

MATERIALS AND METHODS

This guideline was created in line with the Grading of Recommendations Assessment, Development, and Evaluations (GRADE)[8] and Medical Information Distribution Service (MINDS) Handbook for Clinical Practice Guideline Development 2016 and 2020.[9] In addition to a multidisciplinary approach, treatment and care for the prevention of onset and exacerbation of EV require decision making that accounts for the values and intentions of patients and their families. Therefore, this guideline was created via multidisciplinary collaboration of the Japanese Society of Cancer Nursing (JSCN), Japanese Society of Medical Oncology (JSMO), and Japanese Society of Pharmaceutical Oncology (JASPO). The members of the three associations were surveyed about significant clinical challenges related to EV, and 17 clinical questions (CQs) were formulated (Table 1). An algorithm was created to depict the practices implemented by the health care provider for the prevention of onset, early detection, and treatment or care of EV in patients receiving anticancer drugs (Figure 1). This guideline is intended for use by medical staff, patients, and their families.

Details of guideline development including systematic review are provided in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2024.103932. Literature search was mostly carried out from March to April 2021. At the time of literature review, we aimed to distinguish between 'extravasation', which refers to the extravascular leakage of anticancer drugs and 'infiltration', which refers to the leakage of other drugs. For most of the CQs, we could not find strong evidences. To provide the basement of discussion between medical professionals and patients, or among international colleagues, we preferred to set some direction. For that purpose, we applied the evidence-to-decision framework.[8]

Tissue injury was classified as follows. The current guideline adopted the National Health Service (NHS)-England EXTRA,[6] Oncology Nursing Society (ONS),[7] and European Society for Medical Oncology-European Oncology Nursing Society (EONS[5]) tissue injury classifications for 36 drugs for which the three guidelines were consistent. Four independent reviewers conducted a systematic review of 31 drugs (19 drugs with different classifications according to the three guidelines and 12 drugs that required classification according to a survey of the members of the JSCN, JSMO, and JASPO). The PubMed and ICHUSHI Web databases were used for the search. Literature search was carried out on 23 March 2022. Articles were selected using the search terms 'extravasation', 'injection-site reaction', 'adverse events', and the names of individual drugs as keywords. Tissue injury was classified as vesicant, irritant, or non-vesicant according to the definitions provided (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103932). When tissue injury in multiple reported cases was caused by vesicants or irritants, the guideline panel held a discussion to make the decision.

RESULTS

CQs and recommendations

The recommendations posited in this guideline were determined by a guideline panel based on the results of a systematic review of the 17 CQs. The recommendation, strength of recommendation, certainty of evidence, harm, benefits, and consensus rate are shown in Table 1.

1a. Prevention of EV

[CQ1] Patient education. Recommendation (RC): No recommendation (no vote).

The following benefits were identified: 'decrease in ulcers/necrosis' from a case report,[10] 'decrease in the frequency of EV' from a practice report ,[11] and 'increase in the frequency of telephone consultations' from a qualitative study,[12] all of which were indirect. The balance between benefit and harm was 'unknown' and the certainty of evidence was determined to be 'very low'. Therefore, there were no recommendations regarding patient education.

[CQ2] Device selection: central venous (CV) device [CV catheter, peripherally inserted central catheter (PICC), or CV port] placement. RC: It is weakly recommended to place a CV device in patients planning to receive anticancer drugs.

'Reduction of administration failure', a benefit, was investigated in one randomized controlled trial (RCT), which reported a significant decrease in administration failure with a CV port compared to a peripherally inserted catheter.[13] No controlled trials investigated the harm. Although the quality of the evidence was high, the certainty of the evidence was rated as 'moderate' because there was only

Table 1. Clinical questions and recommendations

Clinical questions		Recommendation	Desirable outcomes (benefit)	Undesirable outcomes (harm)	Balance between desirable and undesirable outcomes	Recommendation (strength)[a]	Certainty of evidence[b]	Consensus rate
CQ1	Is multiple patient education regarding extravascular invasion recommended for patients receiving anticancer drugs via peripheral or central veins?	No recommendation	Unidentified (probably decreased ulceration and necrosis, decreased EV, and increased telephone consultation)	Unidentified (probably increased medical staff workload)	Not evaluable	None	D	No voting
CQ2	Is placement of a central venous device (CV catheter, PICC, CV port, etc.) recommended in patients scheduled to start anticancer drugs?	CV devices are weakly recommended	Completion of scheduled administration, less pain and anxiety from cannulation	Device complications (8%)	Central venous device is beneficial	Recommend (weak)	B	9/9 (100%)
CQ3a	Which central venous catheter (CV catheter or PICC) is recommended for cancer patients?	PICC is weakly recommended	Decreased complications such as catheter removal, infection, and thrombus	Unidentified	PICC is beneficial (limited to leukemia patients)	Recommend (weak)	B	9/9 (100%)
CQ3b	Which central venous devices, CV catheter or CV port, is recommended for patients with cancer?	CV port is weakly recommended	Decreased device failures, infections, and complications	Thrombus	CV port is beneficial	Recommend (weak)	B	9/9 (100%)
CQ3c	Which central venous device, PICC or CV port, is recommended for patients with solid tumors?	CV port is strongly recommended	Decreased device failures, infections, and complications	Unidentified (probably medical costs)	CV port is beneficial	Recommend (strong)	A	9/9 (100%)
CQ4	Is it recommended that peripheral intravenous catheters for the administration of anticancer drugs be placed more centrally than at the puncture site?	Central (upstream) placement is weakly recommended	Decreased EV, decrease in skin ulceration at the site of EV	Unidentified (probably decreased puncture vessel options)	Central (upstream) placement is beneficial	Recommend (weak)	C	8/9 (89%)
CQ5	Is routine replacement of peripheral venous catheters recommended to prevent extravasation in patients receiving continuous (intermittent) administration of anticancer drugs?	Not to do routine replacement is weakly recommended	Decreased EV, decreased phlebitis, decreased skin inflammation due to adhesive plaster	Unidentified (probably increased patient distress, increased medical staff workload)	Routine replacement is harmful	Not recommend (weak)	C	9/9 (100%)
CQ6	Is free flow recommended over an infusion pump as a method of administration to prevent extravasation?	Balance between strict rate control and EV prevention; free flow is weakly recommended/when strict rate control is required, not to do free flow is weakly recommended.	Decreased EV, decreased skin inflammation, prevention of skin ulceration (necrosis)	Unidentified (probably decreased accuracy of dose rate control, increased medical staff workload)	Unless strict rate control is required, infusion pump is weakly discouraged	Recommend or not recommend (weak)	C	8/9 (89%) (second vote)
CQ7	Is administration of fosaprepitant recommended considering the risk of extravasation of anticancer drugs?	Fosaprepitant administration is weakly recommended (limited to patients who cannot be administered orally)	Inhibiting nausea and vomiting	Increased EV and injection-site reactions	Fosaprepitant or aprepitant use is beneficial	Recommend (weak)	C	9/9 (100%)

Continued

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Table 1. Continued

Clinical questions		Recommendation	Desirable outcomes (benefit)	Undesirable outcomes (harm)	Balance between desirable and undesirable outcomes	Recommendation (strength)[a]	Certainty of evidence[b]	Consensus rate
CQ8	Is it recommended to check blood backflow for early detection of extravasation?	Checks for blood backflow is weakly recommended.	Early detection of EVs, detection of indwelling needle location and breakage, confirmation of intravascular placement, reduction of skin damage (redness and swelling)	Unidentified	Check blood backflow is beneficial	Recommend (weak)	D	9/9 (100%)
CQ9	Is suction of residual drug solution or blood recommended to prevent exacerbation of skin injury in the event of extravasation?	No recommendation	Decreased areas of skin injury (redness and swelling), pain, ulcers, and shortened recovery days	Unidentified (probably damage to blood vessels due to suction)	Not evaluable	None	D	No voting
CQ10a	Is cold compression recommended as local therapy to prevent aggravation/ progression of skin injury and inflammation induced by extravasation?	Cold compression is weakly recommended	Decrease in inflammation (dermatitis and vasculitis), pain, and burning sensation at the site of leakage, and shortened recovery days	Skin damage (burns) and exacerbation of inflammation due to low or high temperatures	Cold compresses is beneficial	Recommend (weak)	D	9/9 (100%)
CQ10 b	Is warm compression recommended as local therapy to prevent aggravation/ progression of skin injury and inflammation induced by extravasation?	Non-use of warm compresses (heat) is weakly recommended			Hot compresses is harmful	Not recommend (weak)	D	9/9 (100%) (second vote)
CQ11	Is the use of dexrazoxane recommended for extravasation induced by anthracycline cancer drug?	Dexrazoxane use is weakly recommended	Decreased surgical procedures (debridements and skin grafts) and shorter recovery days	Dexrazoxane side-effects, hospitalization, and prolongation of hospital days	Dexrazoxane use is beneficial	Recommend (weak)	B	8/8 (100%)
CQ12	Is local steroid injection recommended for extravasation caused by anticancer drugs?	Not injecting local steroid is weakly recommended.	Decreased surgical procedures (debridements and skin grafts) and shorter recovery days	Local skin damage, local injection pain	Local steroid injection is harmful	Not recommend (weak)	D	9/9 (100%)
CQ13	Is topical steroid recommended for extravasation caused by anticancer drugs?	Topical steroid application is weakly recommended	Decreased surgical procedures (debridements and skin grafts) and shorter recovery days	Skin damage at the application site (infection, skin atrophy)	Topical steroid application is beneficial	Recommend (weak)	D	9/9 (100%)
CQ14	Is debridement recommended for skin ulcers without necrosis due to extravasation?	Not to do debridement is weakly recommended	Skin ulcer healing	Skin invasions	Debridement is harmful	Not recommend (weak)	C	9/9 (100%)

CV, central venous catheter; CQ, clinical question; EV, extravasation; PICC, peripherally inserted central venous catheter.

[a]Recommend (strong): strongly recommended to do, recommend (weak): weakly recommended to do, not recommend (strong): strongly recommended not to do, not recommend (weak): weakly recommended not to do.

[b]A: High—evidence is a great certainty close to the true effect; B: Moderate—evidence is moderately confident of true effectiveness; C: Low—evidence is limited in its certainty of true near-effect (true effects may differ greatly from evidence estimates); D: Very low—evidence is far from convincing of a true effect (true effects differ significantly from evidence estimates).

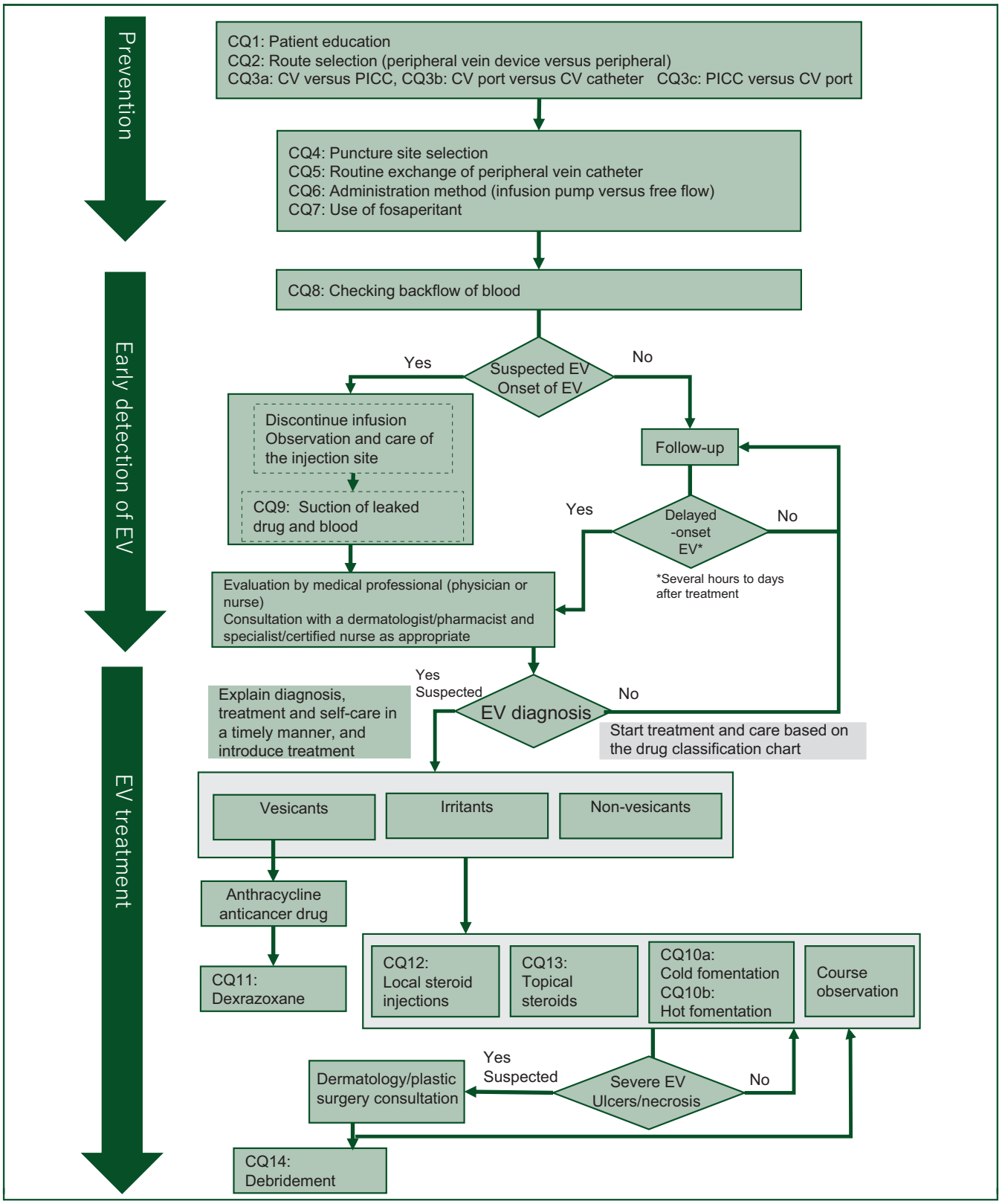

Figure 1. Algorithm of clinical care related to EV. It depicts the role of each CQ in the algorithm of clinical care of EV, such as prevention, early detection, and treatment.
CV, central venous catheter; CQ, clinical question; EV, extravasation; PICC, peripherally inserted central venous catheter.

one study. Based on this evidence, placement of a CV device in patients planning to receive anticancer drugs is rated as a weak recommendation.

[CQ3] Selection of a CV device. The chosen outcome was device failure (obstruction, infection, thrombosis, or removal). Seven RCTs comparing three devices (two CV

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catheter versus CV port, four PICC versus CV port, and one PICC versus CV catheter) were included.

1) [CQ3a] Selection of CV catheter or PICC. RC: PICC is weakly recommended in patients with cancer, compared with CV.

One RCT that investigated patients with leukemia receiving induction anticancer chemotherapy[14] found that the frequencies of catheter-related infections or thrombi and device failures were significantly lower in the PICC group. Based on this evidence, PICC is weakly recommended over CV catheters as a CV device in patients with cancer. However, because this study included only patients with leukemia, the certainty of the evidence for patients with cancer overall was rated as 'moderate'.

2) [CQ3b] Selection of CV catheter or CV port. RC: CV port is weakly recommended in patients with cancer, compared with a CV catheter.

Two RCTs, one investigating patients with solid cancer[15] and another investigating patients with acute leukemia,[16] were extracted. The occurrence of device failure in patients with solid cancer was lower among those with CV ports. However, although complications were more frequent with the use of CV ports in patients with acute leukemia, there was a risk of bias due to numerous exclusions; therefore, the certainty of evidence was rated as 'moderate'. Therefore, a CV port is weakly recommended over a CV catheter in patients with solid cancer.

3) [CQ3c] Selection of PICC or CV port. RC: CV port is strongly recommended in patients with solid tumors, compared with a PICC.

Four RCTs examining PICCs in patients with solid cancer were extracted. Studies on device failure were limited to one RCT, and the failure rate was significantly lower with the use of CV ports.[17] A meta-analysis of other outcomes, including infection, thrombosis, and post-device complications, was reported in all four trials, and these outcomes were significantly less frequent among patients with CV ports.[18-20] Although there was only one RCT investigating device failure, the results of complications were consistent across multiple RCTs; therefore, the certainty of evidence was rated as 'high'. Placing a CV port over a PICC in patients with solid tumors is strongly recommended.

[CQ4] Site of peripheral venous catheter placement after puncture procedure. RC: It is weakly recommended to place a peripheral venous catheter centrally (upstream) from the site of preceding puncture for patients receiving anticancer drug therapy from the peripheral veins.

One cohort study was extracted, which reported a 'decrease in EV', with a catheter placed in a more upstream peripheral vein.[21] The certainty of evidence was considered 'low' as only one infiltration event was reported. Therefore, the recommendation is rated as weak.

[CQ5] Routine replacement of peripheral venous catheters. RC: It is weakly recommended not to replace peripheral venous catheters with specific time interval in patients receiving anticancer drugs.

One meta-analysis and one RCT were extracted focusing on the benefit 'decrease in EV'.[22,23] The meta-analysis reported that routine replacement of peripheral venous catheters every 72-96 h resulted in lower infiltration than *ad hoc* replacement, but not lower EV, as determined by clinical symptoms.[22] In contrast, the RCT evaluated EV and found no difference in its incidence based on placement of peripheral venous catheters.[23] The certainty of evidence was rated as 'low' owing to indirectness caused by inclusion of infiltration among the outcomes. Since there is clear harm associated with peripheral venous catheter replacement (pain for the patient and burden for the medical staff), it was deemed that the harm outweighed the benefit. Therefore, periodic replacement of peripheral venous catheters in patients receiving anticancer drugs is weakly discouraged.

[CQ6] Avoidance of infusion pump. RC: Unless strict dose rate control is required, avoidance of infusion pump is weakly recommended when administering anticancer drugs via the peripheral vein.

One cohort study[24] and six case reports[25-30] investigated desirable outcomes, such as 'decrease in EV', 'decrease in skin inflammation', and 'avoidance of skin ulceration (necrosis)'. The cohort study examined infiltration in children and reported the inferiority of the infusion pump. Only the case reports described the incidence of EV/infiltration with use of an infusion pump; therefore, the causal relationship between pump use and EV/infiltration was unclear. The strength of evidence of the cohort study was rated as 'weak' due to indirectness arising from the lack of inclusion of anticancer drugs. Infusion pumps offer superior rate control, and the balance between benefit and harm varies with circumstances such as the level of drug-induced EV injury and the need for dose rate control. Unless strict dose rate control is required, avoidance of infusion pump is weakly recommended when administering anticancer drugs via the peripheral vein.

[CQ7] Administration of fosaprepitant. RC: Fosaprepitant administration with caution for injection-site reactions is weakly recommended.

A meta-analysis of 14 RCTs with 'complete control of vomiting' confirmed the antiemetic efficacy of fosaprepitant.[31-44] Nineteen retrospective studies reported 'vasculitis, vascular pain, and injection-site reaction' with fosaprepitant administration,[45-63] and seven studies reporting the 'leakage of anticancer drugs administered after fosaprepitant' were extracted.[45,48,52,53,62,64] Although multiple studies described EV as an adverse event, none directly examined whether fosaprepitant increases the risk of EV. The certainty of evidence for harm was rated 'low' since the results were derived from retrospective studies. The benefit of fosaprepitant administration as a strong antiemetic was determined to outweigh the harm, but fosaprepitant may increase injection-site reaction.

Therefore, fosaprepitant administration with caution for injection-site reactions is weakly recommended.

1b. Early detection of EV

[CQ8] Checking blood backflow. RC: Assessing blood backflow for early detection of EV is weakly recommended.

Three case reports assessing 'early detection of EV' were extracted.[65-67] No reports of adverse effects associated with assessing blood backflow were found, given that it is beneficial for verifying the position of the indwelling needle, assessing the presence or absence of occlusion, and confirming that the catheter is in the blood vessel. All extracted studies also mentioned concomitant use of interventions, such as observation of the skin at the puncture site of the indwelling needle, subjective symptoms experienced by the patient, and cessation of infusion. However, the timing and method of blood backflow verification were not clear; hence, the certainty of the evidence was rated as 'low'. Therefore, judging that the benefit outweighs the harm, confirmation of blood backflow for early detection of EV is weakly recommended.

1c. Care at EV onset

[CQ9] Suction of blood or residual drug solution. RC: No recommendation (no vote).

Four studies on 'reduced severity of skin disorders (redness and swelling)', 'reduced skin pain', 'reduced incidence of ulceration', and 'reduced time to recovery of symptoms' were extracted.[68-71] There were only single reports of each outcome, and they were deemed to be weak as evidence for the efficacy of suctioning of blood or residual drug solution alone, as the methods and timing of suction were not described and suctioning was combined with other interventions such as steroid ointment application. The certainty of the evidence was rated as 'very low' owing to a dearth of studies on the harmful outcomes, which did not allow us to weigh the benefit against the harm. Therefore, there was no recommendation regarding the suctioning of residual drug solution or blood to prevent exacerbation of tissue injury in the EV.

[CQ10] Cold and warm compression. The benefits associated with cold and warm compression were 'reduced EV site inflammation (dermatitis/vasculitis)', 'reduced EV site pain/burning sensation', and 'days to recovery of symptoms'. In addition to 'exacerbation (worsening) of the inflammatory reaction', the injuries were 'skin damage due to low temperature' for the cold compression method and 'skin damage due to high temperature' for warm compression.

[CQ10a] Cold compression. RC: Cold compression is weakly recommended as local therapy to prevent aggravation/progression of tissue injury and inflammation induced by EV.

One case-controlled trial and four case reports on cold compression were extracted.[72-76] These studies demonstrated that cold compression results in reduced inflammation at the site of EV, reduced pain and burning sensations, and fewer days until recovery of symptoms. Inflammatory symptoms did recur after temporary reduction in one report; however, both patients were also treated with steroid ointments and topical compresses. Therefore, we judged that the evaluation of the utility of interventions using cold compression alone was poor, and the certainty of the evidence was rated as 'very low'. Cold compression is effective in reducing pain or inflammation when used in conjunction with other interventions and is noninvasive; therefore, the benefits were deemed to outweigh the risks. Therefore, cold compress is weakly recommended as local therapy to prevent exacerbation or progression of EV.

[CQ10b] Warm compression. RC: Avoidance of warm compresses (heat) is weakly recommended to prevent EV-induced skin damage and aggravation/progression of inflammation.

Since there were no relevant evidences solely studying warm compression in human subjects, one human study and two animal studies were used as references by hand search.

In the human study, subcutaneous injection of hyaluronidase and warm compression to the site of vinorelbine leakage were carried out in addition to the administration of oral antibiotics, which resulted in scarring of erythematous lesions.[77] In an experimental study in mice, warm compression (43-45°C) did not aggravate ulcers that arose after subcutaneous injection of vinca alkaloids.[78] However, another study observed ulceration in all mice that received subcutaneous injection of vincristine followed by warm compression,[79] suggesting the deleterious effect of applying warm compression alone to EV induced by vinca alkaloids. The combination of hyaluronidase and other drugs with warm compression does not cause ulceration and may reduce the inflammatory response, but hyaluronidase is not approved for EV in Japan, and the usefulness of warm compression alone is unknown; hence, the certainty of the evidence was rated as 'very low'. Therefore, the use of warm compression alone as local therapy to prevent aggravation or progression of skin injury or inflammation induced by EV is weakly not recommended.

1d. Treatment for EV

[CQ11] Dexrazoxane. RC: Administration of dexrazoxane for EV induced by an anthracycline cancer drug is weakly recommended.

One observational study and six case studies were extracted.[28,80-85] Regarding the benefit 'decrease in the number of surgical procedures (debridement or skin graft)', administration of dexrazoxane reduced the frequency of surgical procedures.[28,80,81] Furthermore, evaluation of the outcome 'administration of anticancer drugs as scheduled' revealed that treatment was completed according to schedule after the onset of EV.[28,80-85] The data for the harmful outcome 'prolonged hospital stay or visit' varied

across studies[80,83,85] and could not be homogenized. It was also difficult to eliminate the possibility that the adverse reactions were caused by anticancer drugs.[28,80-82,84,85] Moreover, there is a lack of controlled trials of dexrazoxane, and its efficacy for EV of very small volumes is unknown. Therefore, the certainty of evidence was rated as 'moderate', and dexrazoxane administration is weakly recommended for EV induced by anthracycline chemotherapy regimens.

[CQ12] Local steroid injection. RC: It is weakly recommended not to inject local steroids for EV of anticancer drugs.

Seven studies on the 'decrease in surgical procedures',[75,86-91] nine studies on the 'decrease in time to recovery',[75,86-93] and one study on 'skin damage at the fomentation site (local infection, skin atrophy, etc.)' were extracted.[88] There were no studies on 'pain associated with local steroid injection'. The majority of studies were case reports, providing no evidence for local injection of steroids alone. The study by Yamada et al. (M, Yamada, et al. 2016. Conference presentation) compared the severity score and recovery time after vesicant EV between local and non-local steroid injection. The severity score of the local steroid injection group was significantly higher than that of the non-local injection group. Furthermore, the time to recovery was significantly longer in the local steroid injection group. These data suggested the certainty of evidence was 'very low'; therefore, we weakly discourage local steroid injection for EV. A study by Ohisa et al.,[94] which was reported after the guideline was formulated, compared patients who received topical steroids, local anesthetics, and subcutaneous steroids with those who received only topical steroids. The odds ratio for the incidence of skin surgery was significantly higher for patients who underwent subcutaneous steroid injection than for those who underwent topical steroid therapy, supporting the evidence adopted in the guideline.

[CQ13] Topical steroid application. RC: Applying topical steroids for EV of anticancer drugs is weakly recommended.

One study on 'reduction of surgical procedures',[95] nine studies on 'time to recovery',[71,74,75,90,92,95-98] and one study on 'skin disorder at the fomentation site (local infection, skin atrophy, etc.)'[97] were extracted. All were case reports; none reported monotherapy with topical steroid application but rather reported its use combined with another intervention. The certainty of evidence was rated as 'very low'. However, since its efficacy in combination with other interventions was demonstrated, it was judged to be effective based on indirect evidence. In general, the use of topical steroids for the purpose of inflammation control at EV sites is considered effective, and judging that the benefit outweighs the harm, topical application of steroids to EV sites is weakly recommended.

[CQ14] Debridement. RC: It is weakly recommended not to debride EV-induced skin ulcer lesions without necrosis.

Five observational studies were extracted.[99-103] Surgical and conservative therapies within 72 h of leakage of drugs other than anticancer drugs were compared for the beneficial outcome of 'healing of skin ulcer', and both elicited good results.[99] Other studies reported the efficacy of surgical procedures for ulcerous lesions; however, they did not describe the timing of ulcer development or their conditions.[100-103] 'Postoperative sequelae', a harmful outcome, was unevaluable for ulcers without necrosis. The certainty of evidence was classified as 'low'. Skin ulcers without EV-induced necrosis may be cured even with conservative treatment. Therefore, the disadvantages of uniformly recommending debridement were deemed to outweigh the advantages. Given the characteristic of EV-related tissue injury, i.e. its origin in subcutaneous tissue, estimating the extent of tissue damage early and determining the depth of debridement is challenging. Therefore, for EV-induced skin ulcer lesions without necrosis, it is weakly recommended not to debride them.

Tissue injury classification table

The flowchart of the systematic review for EV tissue injury is shown in Figure 2. Ten classifiable drugs were added, such that EV injury caused by 46 drugs was classified (Table 2). Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103932, enumerates the drug classifications of the three previous guidelines and the present systematic review.

Of the 10 drugs, amrubicin, oxaliplatin, docetaxel, paclitaxel, mitoxantrone, and ranimustine were classified as vesicants because of reported EV-related necrosis in humans and necrotic anticancer drug-related symptoms (Supplementary Table S3,[70,72,73,86,104-134] available at https://doi.org/10.1016/j.esmoop.2024.103932).

Bleomycin had only been reported to cause inflammatory reactions, even after intradermal injection, and was classified as an irritant. Methotrexate was classified as a non-vesicant drug because local reactions to subcutaneous injection were limited to erythema and crusts.

Necrosis was observed in all studies of cyclophosphamide, but the effects of concomitant drugs could not be ruled out as the patients were receiving combination therapy with anthracycline anticancer drugs.[113-115] Therefore, it was conditionally classified as an inflammatory anticancer drug, under the caveat that it could become a vesicant in the event of EV owing to cyclophosphamide administered after an anthracycline anticancer drug.

Blistering[71] and grade 3 EV requiring surgical intervention due to ulceration or necrosis[132] have been reported with fluorouracil, but the effects of regimens requiring long-term and high-dose administration of fluorouracil cannot be ruled out. Therefore, fluorouracil was conditionally classified as an irritant, under the caveat that it could become a vesicant in the event of long-term administration or large quantities of EV.

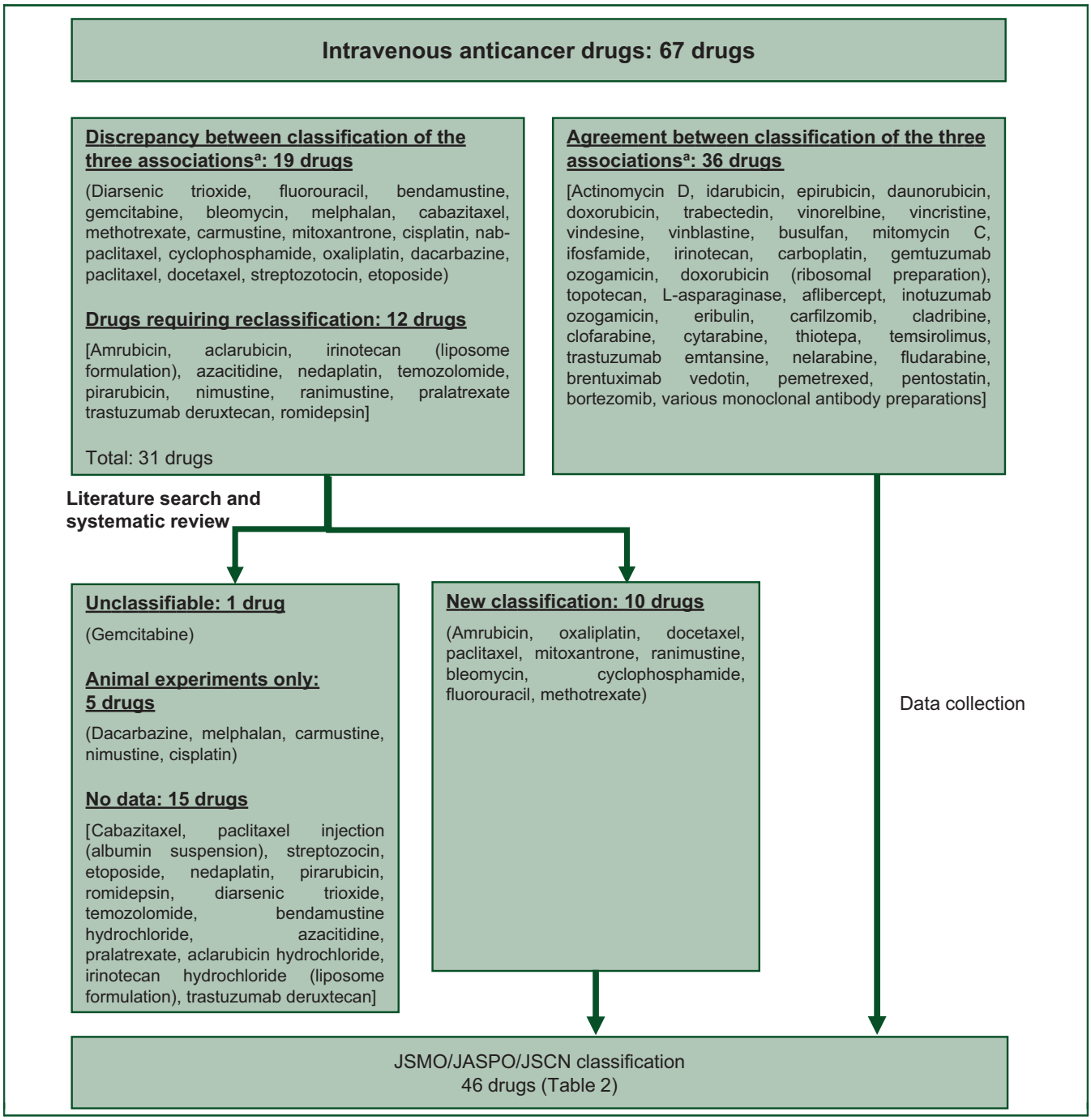

Figure 2. Flow of the systematic review on EV drug classification. Oncology Nursing Society ([a]ONS); Chemotherapy and Immunotherapy Guidelines and Recommendations for Practice [2019, ESMO-European Oncology Nursing Society (EONS)]; Management of chemotherapy extravasation: ESMO — EONS Clinical Practice Guidelines (2012), National Health Service (NHS)-England EXTRA Guidelines for the Management of Extravasation of a Systemic Anti-Cancer Therapy including Cytotoxic Agents (Last update: 2018, Review date: 2020).
JSMO, Japanese Society of Medical Oncology; JASPO, Journal of Japanese Society of Pharmaceutical Oncology; JSCN, Japanese Society of Cancer Nursing.

DISCUSSION

This JSCN/JSMO/JASPO EV guideline addressed 17 CQs related to the prevention, early detection, treatment, and care of EV. This guideline is based on a systematic review and meta-analysis conforming to GRADE/MINDS 2020. Further, we conducted a systematic review on 31 drugs for which there was no consensus among existing guidelines or new drugs with insufficient evaluation regarding the classification of the potential of leaked anticancer drugs to cause damage to surrounding tissues, and a classification with 10 additional drugs was proposed. Among the 17 CQs, recommendations based on the results of RCTs were made with regard to the selection of CV devices (CQ2, CQ3a, CQ3b, and CQ3c), regular replacement of peripheral venous catheters (CQ5), and administration of fosaprepitant (CQ7). These CQs are novel and were not mentioned in previous

Table 2. Drug classification table

Vesicants	Irritants	Non-vesicants
Actinomycin D	Ifosfamide	L-asparaginase
Idarubicin	Irinotecan	Aflibercept
Epirubicin	Carboplatin	Inotuzumab ozogamicin
Daunorubicin	Gemtuzumab ozogamicin	Eribulin
Doxorubicin	Doxorubicin (ribosomal preparation)	Carfilzomib
Trabectedin	Topotecan (nogitecan)	Cladribine
Vinorelbine	Bleomycin[a]	Clofarabine
Vincristine	Cyclophosphamide[b]	Cytarabine
Vindesine	Fluorouracil[c]	Thiotepa
Vinblastine		Temsirolimus
Busulfan		Trastuzumab emtansine
Mitomycin C		Nelarabine
Amrubicin[a]		Fludarabine
Oxaliplatin[a]		Brentuximab vedotin
Docetaxel[a]		Pemetrexed
Paclitaxel[a]		Pentostatin
Mitoxantrone[a]		Bortezomib
Ranimustine[a]		Various monoclonal antibody preparations
		Methotrexate[a]

JASPO, Japanese Society of Pharmaceutical Oncology; JSMO, Japanese Society of Medical Oncology; JSCN, Japanese Society of Cancer Nursing.
[a]Classification according to the systematic review by JSMO/JASPO/JSCN.
[b]Potential vesicant when combined with anthracycline anticancer agents.
[c]Potential vesicant in prolonged therapy and large doses.

guidelines. Several practices that have been instituted conventionally without clear evidence, such as warm compression monotherapy (CQ10b) and local injection of steroids (CQ12), were investigated based on the best available evidence, and consequently, their use is discouraged for the management of EV.

Compared with the four preceding guidelines regarding EV, NHS and ONS guidelines classified agents by DNA binding or non-DNA binding, speculated by the pharmacological background. As far as the systematic research carried out in this guideline is concerned, we could not identify clinical evidence to support this classification. Also, the ESMO-EONS guideline recommended warm compression to vinca alkaloids, taxane, and platinum salts and hyaluronidase to vinca alkaloids and taxane. Our systematic review identified evidence to support warm compression with hyaluronidase only for vinca alkaloids and no clinical evidence to support warm compression monotherapy. Rather, evidences in mice suggest potential harm of warm compression monotherapy for vinca alkaloids EV. Because neither dimethyl sulfoxide (DMSO) nor hyaluronidase are approved in Japan, our guideline recommended to avoid warm compression monotherapy. Also, we recommended to avoid topical injection of steroids and this is compatible with the ESMO guideline. As a result, our approach to EV became very simple, which is applicable to many countries even with restriction for medical resources. Another novel topic of this guideline is refutation to devices for the prevention of EV (for CV devices, CQ2, CQ3a, CQ3b, CQ3c, and for pomp, CQ6).

The main limitation of this guideline is that the best available evidence for many CQs was obtained from case reports and relatively small retrospective studies. Moreover, even in the prospective studies, some important factors which can influence the device choice such as the goal of therapy (curable or palliative), costs, and burden for the medical staff, are scarcely reported. Hopefully, future studies in this field capture and report these data. Another limitation is the lack of recommendation regarding antidotes, because hyaluronidase or DMSO are not approved in Japan. The limitations for drug classification include small sample size, reporting bias, and effect of confounding factors such as combined treatment with other anticancer drugs or treatment for EV. Some drugs such as gemcitabine may increase risk of EV following drugs.[74] There is an urgent need for accumulation of well-designed clinical studies in this field. Another limitation is the focus on EV in the peripheral veins, not for EV from CV devices. This was based on questionnaires filled out by the members of JSCN/JSMO/JASPO. This could change in the future as a result of the adaptation of this guideline, which recommends CV devices.

In conclusion, we provided a guideline for EV management based on a systematic review with a multidisciplinary approach. Currently we are in the process of evaluating the adaptation of this guideline and developing further refined guidelines in collaboration with the JSCN/JSMO/JASPO working group. We hope this guideline will help health care providers and patients and their families in practicing better EV management.

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